PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Incidence of Eating Disorders in the UK in 2000-2009: findings from the General Practice Research Database
AUTHORS	micali, nadia; Hagberg, Katrina; Petersen, Irene; Treasure, Janet

VERSION 1 - REVIEW

REVIEWER	Frederique R.E. Smink, MD Parnassia Psychiatric Institute The Hague, The Netherlands No competing interests.
REVIEW RETURNED	18-Feb-2013

GENERAL COMMENTS	First of all, I would like to compliment the authors on their well-written, concise article on a high-quality dataset, with clear and supportive tables and figures. However, in my opinion, some minor revisions would add to the clarity and strength of the paper. COMMENTS AND SUGGESTIONS: **Method:** Page 5: Line 22-27: *The comprehensive….research*. This sentence is more or less (accidentally?) repeated in the next paragraph (see line 43). I would suggest to remove it in line 22-27, because it says more about the validity of the diagnoses than about the sample. Page 5, line 55 and *page 6*, lines 3-5: I would suggest to move this information to the 'Sample' paragraph of the Method. Page 6: Line 17: *We used….on request*. I would suggest to move this sentence to the next paragraph, before or after the first sentence: *'Cases were…was recorded.*' (line 36).

	Line 27-31: *Information on…computerized record)*. What was the goal of this procedure? Quality control? Validation of diagnosis? Page 6 line 58 and page 7 line 3-8: *If neither….AN and BN.* An interval of 1 month is rather short to distinguish different ED diagnoses. A diagnosis of both AN and BN with a required minimum of just 1 month in between would in my opinion only count as 1 (one) incident ED-case, in which I would include for IR calculation exclusively the diagnosis highest in the hierarchy of ED (i.e. AN). Another option would be to increase the minimum amount of time between diagnoses (eg. 1 year), in which case both diagnoses could be included in IR calculation. However, considering the very low number of cases with a two ED diagnoses (25), with probably an even lower number of diagnoses with a 1-month-interval in between, I understand that this subgroup does not influence IRs much. **Results:** Page 8: Question: are the 73 cases with a co-occurring ED diagnosis included in the aforementioned number of 9,062 patients? Page 8; line 33-39: No of cases: 2,134 + 3,433 + 3,505 = 9072 cases. How does this number relate to the 9,062 patients mentioned in page 8, line 12 of which 25 supposedly have a double diagnosis (and are counted twice as incident cases)? That would add to 9,062 +25 = 9,087 cases. Page 9, line 8-13: *'there was evidence…aged 10-49…'*. This statement might be a little confusing as it suggests that the IR of all ED, meaning the IR of AN, the IR of BN and the IR of EDNOS steadily increased. According to Figure 1, only the IR of EDNOS seems to have increased, while the IR of AN and BN remained stable, as is also mentioned a few lines below. Table S1: I would suggest to keep the same order of presenting results throughout the paper: First females, then males, as is done in the other tables and figures of the article.

	Page 9, about line 38/39 and Page 10: Last sentence (line 50-53): Discrepancy between IR EDNOS in females in 2009 in text and Table S1: 27.6 (text) vs. 27.7 (Table S1). Page 11; last line 1st paragraph (about line 17): Discrepancy between 95%CI in text and TableS1: 95% CI: 3.1-5.4 (text) vs. 95% CI: 3.1-5.3 (Table S1). **Discussion:** Page 13: line 38: I'm not sure, but could it be that 'to' is missing in the following sentence? *'There is evidence that true rates might be double or triple **to** those detected in a health care setting.'*

REVIEWER	Angela Favaro Professor of Psychiatry at Dept. Neurosciences University of Padova, Italy I report no conflict of interest
REVIEW RETURNED	26-Feb-2013

GENERAL COMMENTS	This is a well written paper on a very important (and difficult to study) topic. I have only few minor concerns to suggest before recommending publication. 1. Although previous studies demonstrated a high validity of ED diagnosis made by GP, I wonder if these estimations included EDNOS. EDNOS diagnosis is very poorly defined by DSM-IV and criteria of clinical relevance for 'mild' cases are not available. I think that authors should better discuss this point and its possible implications. 2. Is it information about referral to ED units (or inpatient treatments) available? 3. Although BMI was reported only in 10% of case, did GP report about overweight/obesity conditions associated or preceding eating disorders? Is obesity more frequent in EDNOS subjects? 4. In the conclusions, it is not clear why authors compared incidence rates of EDs with those of type 1 and 2 diabetes. Is, on the contrary, possible to estimate the incidence of EDs in patients with diabetes? An unsolved question of ED epidemiology is how much diabetes represents a risk factor. 5. Did age at diagnosis show any changes over the 10 years considered? Recent research has shown a trend towards decreasing age of onset of both AN and BN. Although age of onset is not available in this study, it would be interesting to study any changes in age at diagnosis.

REVIEWER	Paulo P. P. Machado, Ph.D. Professor Universidade do Minho

	PORTUGAL I have read and understood the BMJ Group policy on declaration of interests and have no relevant interests to declare.
REVIEW RETURNED	27-Feb-2013

GENERAL COMMENTS	The paper describes a primary care register based epidemiological study of Eating Disorders. The aim was to estimate annual (age-, gender-, and subtype-specific) incidence of diagnosed ED: anorexia nervosa, bulimia nervosa and eating disorder not otherwise specified (EDNOS) in primary care over a ten-year period in the UK (2000-2009) The paper is well written, and informative. And the data clearly. One can't but agree with the importance of the findings as reflecting the public health impact of what may appear to be under-recognised eating disorders (EDNOS). I just have a major concern. Given the high prevalence of EDNOS found, it would be important for the authors to also state the diagnostic criteria that they used for EDNOS, as the DSM-IV is not specific about this, The ICD 10 in which the authors based their EDNOS diagnosis is not completely similar to the DSM. For example the authors state tha they used ICD-10 "Eating Disorder Unspecified" notation for EDNOS. However ICD-10 codes F50.1 and F50.3 (Atypical AN and Atypical BN) would also be considered EDNOS under DSM-VI. How were these coded in the current study. I would have expected more detailed information on the EDNOS cases Was the fact that DSM-IV does not allow a simultaneous diagnosis of AN and BN considered? On page 7 this is not clear.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

COMMENTS AND SUGGESTIONS:
1. Method:
Page 5:
"Line 22-27: The comprehensive….research. This sentence is more or less (accidentally?) repeated in the next paragraph (see line 43). I would suggest to remove it in line 22-27, because it says more about the validity of the diagnoses than about the sample."
We have removed the sentence as suggested.

2. "Page 5, line 55 and page 6, lines 3-5: I would suggest to move this information to the 'Sample' paragraph of the Method."
We have now moved the lines to page 5 under "sample" as suggested

Page 6:
3. "Line 17: We used….on request. I would suggest to move this sentence to the next paragraph, before or after the first sentence: 'Cases were…was recorded.' (line 36)."
We have moved the sentence about the information used to page 7 first paragraph, as we felt it fitted better after the description of the codes used and diagnoses used.
4. Line 27-31: Information on…computerized record). What was the goal of this procedure? Quality

control? Validation of diagnosis?"
This information was used for quality control (we have added this description to the sentence on page 7-first paragraph).

5. "Page 6 line 58 and page 7 line 3-8: If neither….AN and BN.
An interval of 1 month is rather short to distinguish different ED diagnoses. A diagnosis of both AN and BN with a required minimum of just 1 month in between would in my opinion only count as 1 (one) incident ED-case, in which I would include for IR calculation exclusively the diagnosis highest in the hierarchy of ED (i.e. AN). Another option would be to increase the minimum amount of time between diagnoses (eg. 1 year), in which case both diagnoses could be included in IR calculation. However, considering the very low number of cases with a two ED diagnoses (25), with probably an even lower number of diagnoses with a 1-month-interval in between, I understand that this subgroup does not influence IRs much."
The reviewer is right that this subgroup does not influence IRs much. Also as specified in that same paragraph "If neither BMI nor symptoms were recorded at the time of diagnosis and the two diagnoses were recorded at least one month apart or if BMI or symptoms were consistent with having both AN and BN then the patient was classified as having an incident case of both AN and BN." Only two cases overall had both diagnoses recorded within one month and had no BMI nor symptoms recorded at the time of diagnosis.
Results:
6. "Page 8: Question: are the 73 cases with a co-occurring ED diagnosis included in the aforementioned number of 9,062 patients?"
See reply to 7. below

7. "Page 8; line 33-39: No of cases: 2,134 + 3,433 + 3,505 = 9072 cases.
How does this number relate to the 9,062 patients mentioned in page 8, line 12 of which 25 supposedly have a double diagnosis (and are counted twice as incident cases)? That would add to 9,062 +25 = 9,087 cases."
Thanks very much to the reviewer for identifying a discrepancy in the numbers. We have rerun the analyses and identified a glitch in the program. We have now revised the exact number of new diagnoses identified, i.e. 9,120 of which: 96 were duplicates that were then considered single incident cases (48 individuals), 42 were duplicates that were considered to have two incident diagnoses (hence were kept as two incident cases). The final number of incident diagnoses was 9,072.

8. "Page 9, line 8-13: 'there was evidence…aged 10-49…'. This statement might be a little confusing as it suggests that the IR of all ED, meaning the IR of AN, the IR of BN and the IR of EDNOS steadily increased. According to Figure 1, only the IR of EDNOS seems to have increased, while the IR of AN and BN remained stable, as is also mentioned a few lines below."
We have now changed the sentence to make it clear that the overall incidence of ED increased as is shown in table S1 (see page 9, second paragraph under "females").

9. "Table S1: I would suggest to keep the same order of presenting results throughout the paper: First females, then males, as is done in the other tables and figures of the article."
We have changed the table as suggested.

10. "Page 9, about line 38/39 and Page 10: Last sentence (line 50-53): Discrepancy between IR EDNOS in females in 2009 in text and Table S1: 27.6 (text) vs. 27.7 (Table S1)."
This has now been corrected.

11. Page 11; last line 1st paragraph (about line 17): Discrepancy between 95%CI in text and TableS1: 95% CI: 3.1-5.4 (text) vs. 95% CI: 3.1-5.3 (Table S1).
This has now been corrected.

Discussion:
12. “Page 13: line 38: I’m not sure, but could it be that ‘to’ is missing in the following sentence? ‘There is evidence that true rates might be double or triple to those detected in a health care setting.’”
We have added of to the sentence above

Reviewer 2
This is a well written paper on a very important (and difficult to study) topic. I have only few minor concerns to suggest before recommending publication.
Thank you very much
1. “Although previous studies demonstrated a high validity of ED diagnosis made by GP, I wonder if these estimations included EDNOS. EDNOS diagnosis is very poorly defined by DSM-IV and criteria of clinical relevance for 'mild' cases are not available. I think that authors should better discuss this point and its possible implications.”
We have added a sentence in the limitations about this on page 14 (third line). We agree with the reviewer that GP’s diagnoses of EDNOS might not be as valid as those of AN and BN, however in at least 50% of the cases reviewed for quality control there was indication of either ED symptoms of underweight BMI. Moreover as mentioned in the discussion, page 13 “general practitioners incorporate data from secondary or tertiary care in the GPRD electronic records when patients are referred, therefore it is possible that some diagnoses included in the database were in fact made by psychiatrists”, therefore we have some validators of EDNOS diagnoses.
2. “Is it information about referral to ED units (or inpatient treatments) available?”
This information is available in GPRD and although we did initially investigate referral to secondary and tertiary services in about 10% of the overall sample the results have not been included in the current publication due to space and focus of the article.

3. “Although BMI was reported only in 10% of case, did GP report about overweight/obesity conditions associated or preceding eating disorders? Is obesity more frequent in EDNOS subjects?”
BMI was reported in more than 10% of cases, but we reviewed by hand only 10% of all cases, overall the percentage of EDNOS patients with an overweight/obese BMI amongst those with EDNOS was 33% (similar to Bulimia nervosa); however 50% of those with EDNOS had a BMI recorded. Although it will be extremely interesting to try and understand patient characteristics of those diagnoses with EDNOS, this goes beyond the scope of the current paper and study. It will be interesting to study this in future.

4. “In the conclusions, it is not clear why authors compared incidence rates of EDs with those of type 1 and 2 diabetes. Is, on the contrary, possible to estimate the incidence of EDs in patients with diabetes? An unsolved question of ED epidemiology is how much diabetes represents a risk factor.”
We have now revised the section in the conclusion specified by the reviewer, our aim was to compare the incidence of ED in adolescence across a range of medical and psychiatric disorders, in order to give the reader a perspective. We have now added the incidence rates of depression in adolescent girls in GPRD as a comparison (see page 14 under conclusions).

5. “Did age at diagnosis show any changes over the 10 years considered? Recent research has shown a trend towards decreasing age of onset of both AN and BN. Although age of onset is not available in this study, it would be interesting to study any changes in age at diagnosis.”
Following the reviewer’s suggestion we investigated mean and median age at diagnosis for AN and BN: for AN there was no evidence that mean and median age at first diagnosis changed across years (median age at diagnosis was 19 and did not vary across time), in relation to BN there was some evidence that the median age at first diagnosis slightly increased over the 10 years under study (median age at diagnosis in 2000: 23.5; median age at diagnosis in 2009: 24 years). Although statistically significant ($p=0.02$) we are unsure that this is a clinically relevant increase (only 6 months

higher) and doubtful that including this information will add to the current manuscript. It would be very interesting to study this issue more in detail using data from previous decades, unfortunately we current do not have ethical approval to do this.

Reviewer 3

"The paper describes a primary care register based epidemiological study of Eating Disorders. The aim was to estimate annual (age-, gender-, and subtype-specific) incidence of diagnosed ED: anorexia nervosa, bulimia nervosa and eating disorder not otherwise specified (EDNOS) in primary care over a ten-year period in the UK (2000-2009)"

"The paper is well written, and informative. And the data clearly. One can't but agree with the importance of the findings as reflecting the public health impact of what may appear to be under-recognised eating disorders (EDNOS)."
Thank you.

1. "I just have a major concern. Given the high prevalence of EDNOS found, it would be important for the authors to also state the diagnostic criteria that they used for EDNOS, as the DSM-IV is not specific about this, The ICD 10 in which the authors based their EDNOS diagnosis is not completely similar to the DSM. For example the authors state tha they used ICD-10 "Eating Disorder Unspecified" notation for EDNOS. However ICD-10 codes F50.1 and F50.3 (Atypical AN and Atypical BN) would also be considered EDNOS under DSM-VI. How were these coded in the current study. I would have expected more detailed information on the EDNOS cases"
Thank you for pointing this out. The diagnostic system used by GPs i.e. Read codes is a standard hierarchical classification system used in databases such as GPRD for recording patient medical information in UK primary care settings. Read codes do not directly map to DSM or ICD-10 codes. We have used the codes that do map on "Eating Disorder Unspecified" and have added codes F50.1 and F50.3 (Atypical AN and Atypical BN) for defining EDNOS (and have clarified this on page 6 last paragraph). Overall very few individuals were diagnosed using F50.1 (~65 cases) and F50.3 (~29 cases).

2. "Was the fact that DSM-IV does not allow a simultaneous diagnosis of AN and BN considered? On page 7 this is not clear."
Yes, we took this into account (see reviewer 1 point 5.); we decided to reclassify all individuals who received a diagnosis of AN and BN on the same day as EDNOS also for this particular reason; and used the timeframe of a minimum of one month in-between diagnoses to allow multiple diagnoses of AN and BN. We have tried to make the paragraph slightly easier to understand on page 7. In reality very few individuals fit this particular situation see response to reviewer 1 (point 5) (2 cases received two diagnoses a month apart and 4 cases between 6 and 12 weeks apart).

VERSION 2 – REVIEW

REVIEWER	Dr. Frederique R.E. Smink, MD Parnassia Psychiatric Institute The Hague The Netherlands No competing interests.
REVIEW RETURNED	03-Apr-2013

GENERAL COMMENTS	Thank you for implementing my suggestions. Congratulations on your paper.